Palladium(II) Complexes of *N*-Sulfonylamino Acids. Part 2.[1] Co-ordination Behaviour under Strongly Acidic Conditions

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The ligation of a series of *N*-sulfonylamino acids (H_2L) to Pd^{2+} was investigated by means of d.c. polarography, ^1H NMR and electronic spectroscopy. The first amino acid is found to bind to the metal under extremely acidic conditions, with an apparent pK_{NH} value of about 1, while an additional molecule binds with a pK_{NH} ranging from 3.1 to 3.7 for the different amino acids. These nitrogen-deprotonated complexes appear not to involve carboxylate complexes as stable precursors. Proton NMR spectroscopy indicates the presence of geometric isomers for the $[PdL_2]^{2-}$ species.

By means of d.c. polarography, *N*-sulfonylamino acids were previously found to bind to Pd^{2+} in a bidentate fashion through the carboxylate oxygen and the deprotonated sulfonamide nitrogen at pH values as low as 3.5, giving the species [Pd(LNO)] and $[Pd(LNO)_2]^{2-}$.[2] Investigation at lower pH values, at which equilibria relevant to the formation of the nitrogen-deprotonated species occur, was prevented by chemical reduction of the Pd^{2+} due to the mercury of the electrode. The present paper focuses on the characterization of the low-pH co-ordinative behaviour of these systems through electronic and ^1H NMR spectroscopy. Our goal is to determine whether Pd^{2+} substitutes for the amide nitrogen-bound hydrogen by a mechanism that can be framed in the general picture obtained for other metal ions such as Cu^{2+} and Cd^{2+}, with which this class of ligands forms nitrogen-deprotonated species only at pH values above neutrality. In this mechanism, the ligand *via* its carboxylate group binds the metal at low pH, in so doing preventing metal hydroxide precipitation and allowing closure of the chelate ring through metal co-ordination of the deprotonated amide nitrogen at higher pH.[3,4]

Experimental

Materials.—*N*-(Phenylsulfonyl)glycine, *N*-tosylglycine, *N*-(phenylsulfonyl)-DL-α-alanine, *N*-tosyl-DL-α-alanine, *N*-tosyl-β-alanine, *N*-benzoylglycine, *N*-acetylglycine and *N*-benzyloxycarbonylglycine were twice recrystallized before use. Doubly distilled water was used throughout.

Polarographic Analysis.—Aqueous solutions for the polarographic analysis were prepared by dissolving the solid complexes $Na_2[Pd(LNO)_2]$ (LNO = N,O-co-ordinated amino acid dianion) up to 5×10^{-4} mol dm^{-3} and by adding amino acid in order to obtain amino acid-to-metal molar ratios in the range 2:1 to 20:1. Polarographic measurements were carried out in the range pH 11.5–3.5 by adding small amounts of concentrated aqueous $HClO_4$ (72% w/w) to the starting basic solution. A slow chemical reduction of Pd^{2+} by Hg was detected below pH 3.5 and this prevents any quantitative analysis at these pH values.[2] Sodium perchlorate was used as base electrolyte and the ionic strength was kept constant (I = 0.1 mol dm^{-3}). An Amel 472 Multipolarograph was employed at 25 ± 0.1 °C with a dropping mercury electrode and a platinum sheet as working and counter electrode, respectively. A saturated calomel electrode (SCE) was used as a reference and all the $E_{\frac{1}{2}}$ values are referred to it. A Jenway 3045 Ion Analyser equipped with an Ingold HA 405-60-K1 pH combination electrode was used for pH measurements. The electron-transfer processes were analysed by using concentrations from 1×10^{-4} to 5×10^{-4} mol dm^{-3} Pd^{2+} and dropping times of 1, 2, 3 and 4 s. The reversibility of the processes was determined by semi-logarithmic analysis of the polarographic waves. The $E_{\frac{1}{2}}$ values for quasi-reversible processes were determined according to Matsuda and Ayabe.[5] The dependence of the limiting current on the dropping time and on the depolarizer concentration indicated the diffusive nature of the processes. The number of electrons involved in the reduction of the complexes was determined by means of the Ilkovich equation.

Spectroscopy.—Proton NMR measurements were carried out on a Bruker AMX-400 spectrometer at 400.13 MHz. Typical acquisition parameters were as follows: spectral bandwidth, 5 kHz; pulse width, 6 μs (90° pulse); pulse delay, 4 s; number of scans collected, 256–512. Spectra were run on saturated aqueous (D_2O) solutions of the crystalline complexes at 27 ± 0.1 °C, and are referenced to tetramethylsilane. The residual water peak was suppressed by a presaturation pulse from the decoupler. The pH values were adjusted by adding small amounts of concentrated NaOH or $HClO_4$; pH meter readings are uncorrected for the isotope effect. The UV/VIS spectra were recorded with a Cecil 6606 spectrophotometer on aqueous solutions obtained by dissolving the crystalline complexes. The pH was changed by adding small amounts of concentrated NaOH or $HClO_4$.

Results

Polarography.—The binary systems Pd^{2+}–*N*-(phenylsulfonyl)-DL-α-alaninate (bs-α-ala) and Pd^{2+}–*N*-tosyl-DL-α-alaninate (ts-α-ala) show a polarographic behaviour very similar to that previously observed for the corresponding glycine derivatives.[2] Only one quasi-reversible, two-electron, diffusion-controlled reduction wave is observed between pH 3.5 and 11.5. The half-wave potential ($E_{\frac{1}{2}}$) decreases with increasing amino acid concentration, while the diffusion current (i_d) remains constant. The $E_{\frac{1}{2}}$ and i_d values are pH-independent. In the pH range investigated the amino acids act as *N*,*O*-bidentate dianions, as shown by X-ray crystallography of the solid complexes separated at these pH values.[6,7] The overall stability constants (β), determined with the DeFord–Hume equation,[8] are listed in Table 1. These amino acids invariably give rise to the [Pd(LNO)] and $[Pd(LNO)_2]^{2-}$ species. Lingane plots[9]

Table 1 Values of log β[a] for complexes in aqueous solution, I = 0.1 mol dm^{-3}, 25 °C; the estimated error in log β is ±0.1

	log β	
Ligand L	[Pd(LNO)]	[Pd(LNO)$_2$]$^{2-}$
tsgly[b]	17.8	23.4
bsgly[b]	18.9	24.4
dnsgly[b,c]	17.8	21.8
ts-α-ala	19.9	23.3
bs-α-ala	20.6	23.0
ts-β-ala	16.8	20.5
bs-β-ala	17.1	20.8

[a] β is the overall stability constant. [b] From ref. 2. [c] dnsgly = *N*-(5-Dimethylaminonaphthylsulfonyl)glycinate.

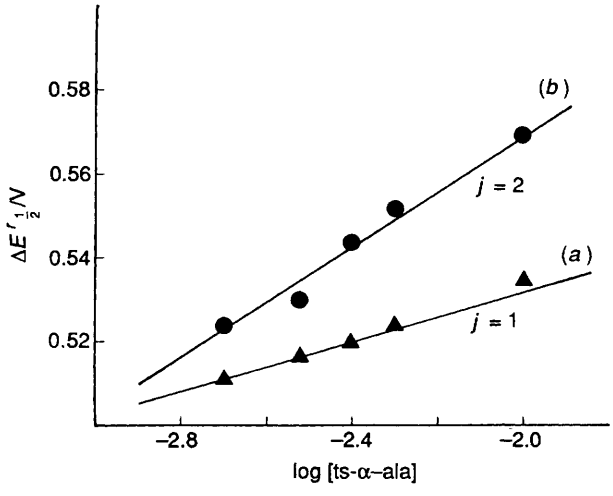

Fig. 1 Plot of $\Delta E_{\frac{1}{2}}{}^r$ *vs.* −log [ts-α-ala] for the binary system Pd^{2+}–ts-α-ala at pH 7.6 [$\Delta E_{\frac{1}{2}}{}^r = E_{\frac{1}{2}}(Pd^{2+}) - E_{\frac{1}{2}}$(complex), where $E_{\frac{1}{2}}(Pd^{2+})$ is the half-wave reduction potential for the solvated Pd^{2+} ion[2] and $E_{\frac{1}{2}}$(complex) is that of the complex]. A similar qualitative trend was observed for the other ligands. pH: (*a*) 3.5, (*b*) 7.0. *j* is the maximum ligand co-ordination number

indicate that the binding of one amino acid molecule is favoured at low pH, while two preferentially co-ordinate with increasing pH (Fig. 1). The polarographic data obtained for Pd^{2+} interacting with *N*-tosyl-β-alanine are qualitatively similar to those described above, but the quasi-reversible, two-electron and diffusion-controlled wave begins to appear at higher pH (about 4) and is displaced toward more positive $E_{\frac{1}{2}}$ values (about 130 mV). Also in this case the analysis of the polarographic data indicates the presence of nitrogen-deprotonated species with stability constants lower by about four orders of magnitude than those of the corresponding species formed by *N*-tosylglycinate (ts-gly) and ts-α-ala (see Table 1). For the glycines N-protected by an acetyl, benzoyl or benzyloxycarbonyl group, only a low-intensity and ill shaped reduction wave is observed in a narrow pH range (3.5–4.2), which quickly disappears at higher pH values due to metal hydroxide precipitation. Such behaviour prevents any reliable analysis of the species involved in the reduction process.

Electronic Spectra.—The UV/VIS spectra of the crystalline complexes dissolved in aqueous solution show a very similar pH dependence. For example, the spectral features of [Pd(ts-α-alaNO)$_2$]$^{2-}$ are shown in Fig. 2. The limiting spectrum at low pH is characteristic of the solvated Pd^{2+} ion.[10] With increasing pH two bands appear at 430 and 365 nm following a typical titration pattern. A first limiting spectrum is reached at about pH 1.9 [Fig. 2(*a*)]. With further increase in pH the band at 430 nm decreases in intensity while that at 365 nm becomes less

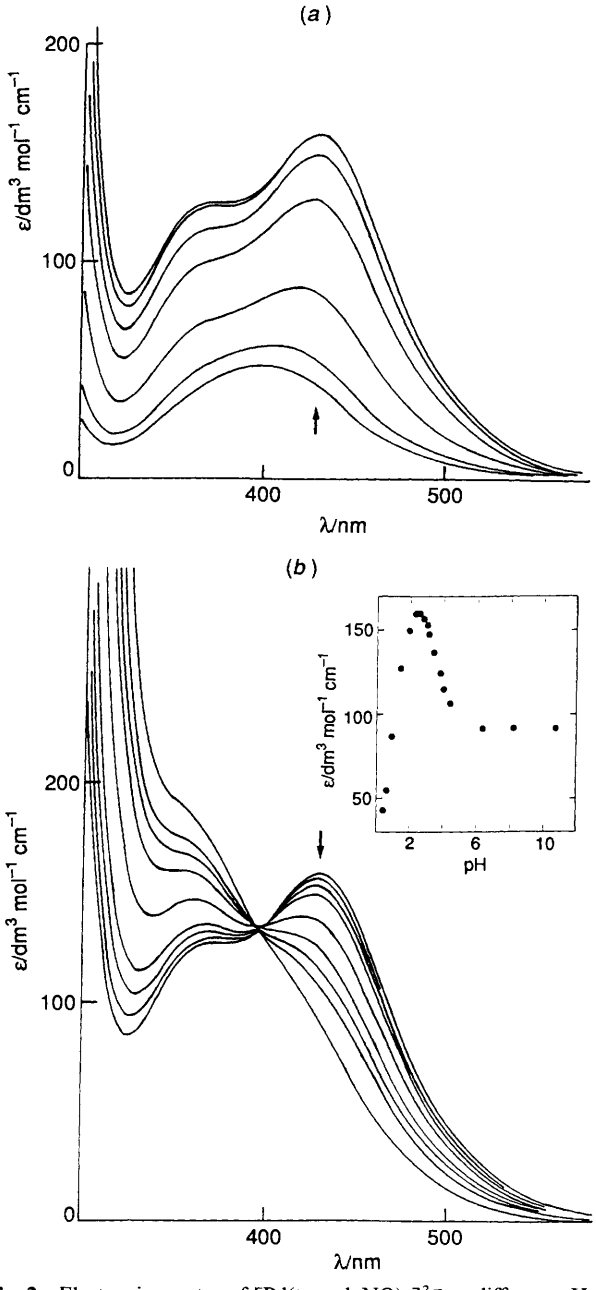

Fig. 2 Electronic spectra of [Pd(ts-α-alaNO)$_2$]$^{2-}$ at different pH: (*a*) 0.44, 0.60, 0.95, 1.39, 1.96, 2.32 and 2.61, in order of increasing molar absorption coefficient ε at 430 nm, as indicated by the arrow; (*b*) 2.61, 2.81, 3.0, 3.12, 3.43, 3.77, 4.03, 4.43, 6.33, 8.14 and 10.68, in order of decreasing ε at 430 nm (see arrow). The curves for the last three pH values are overlapped. The inset in (*b*) shows the overall pH dependence of ε at 430 nm and 296 K

resolved apparently due to the increase in intensity of the ligand spectral envelope. This spectral change is clearly due to an equilibrium between two species, with an apparent pK_a value of 3.6, as indicated by a well defined isosbestic point at 393 nm. The limiting spectrum at high pH is almost featureless: it contains a shoulder at 360 nm, while the band at 430 nm has almost disappeared. The inset in Fig. 2(*b*) shows a plot of the molar absorption coefficient at 430 nm *vs.* pH. Overall, these spectra are indicative of the presence of two equilibria with apparent pK_a values of about 1 and 3.6. While pK_{a1} remains the same for all the amino acids, pK_{a2} values of 3.1 and 3.4 have been observed for bs-α-ala and the *N*-substituted glycines, respectively. The spectral change corresponding to the first equilibrium is not consistent with the persistence of an all-

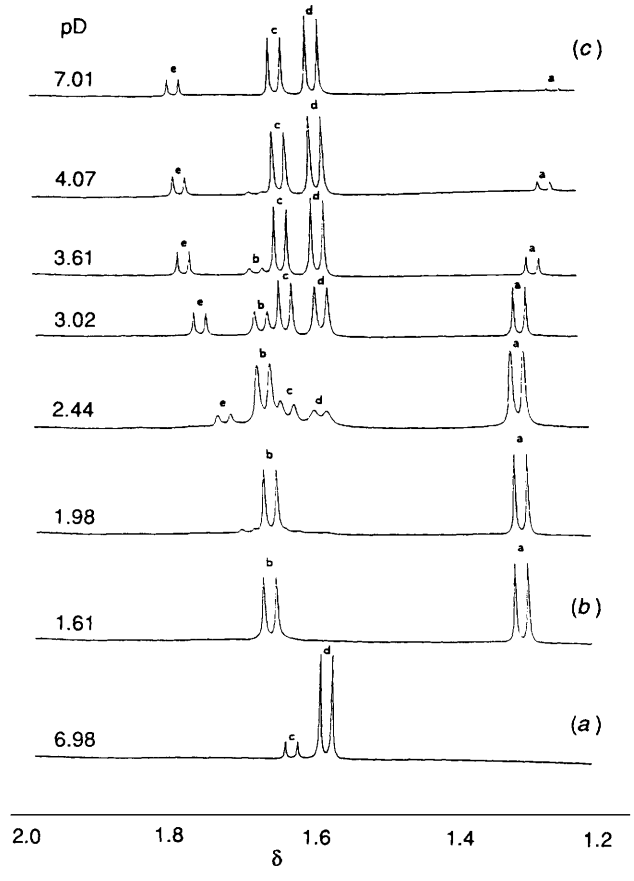

Fig. 3 Low-frequency region of the 400 MHz ^{1}H NMR spectrum of $[Pd(bs\text{-}\alpha\text{-}alaNO)_2]^{2-}$ in D_2O taken at different pD values

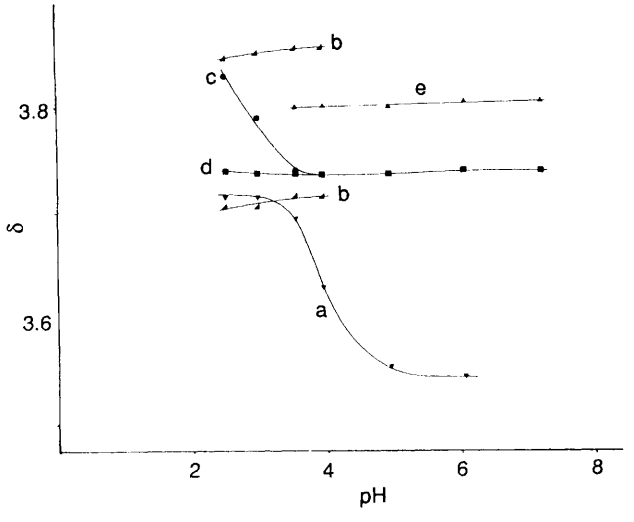

Fig. 4 The pH dependence of the ^{1}H NMR resonances of the glycine moiety in the 400 MHz ^{1}H NMR spectrum of $[Pd(bsglyNO)_2]^{2-}$ in D_2O

oxygen metal chromophore, as would be the case for exclusive formation of carboxylate complexes, which typically constitute the low-pH species formed by this class of ligands interacting with a number of bipositive metal ions. Instead, it is indicative of the involvement of nitrogen in metal co-ordination, hence of the formation of a species containing a nitrogen-deprotonated ligand, even at these very low pH values. In particular, this is most probably a species in which only one molecule of *N,O*-bidentate dianion binds to the metal, as is also suggested by the above polarographic data which indicate it to be preferred over the complex containing two co-ordinated amino acid molecules at the lowest pH accessible for the measurements. The equilibrium between these two species is reasonably responsible for the second titration pattern in the spectra: the overall shift of the band maximum toward higher energies with increasing pH is consistent with the involvement of one more nitrogen in the metal chromophore. These spectra do not rule out the existence of simple carboxylate species as precursors of the nitrogen-deprotonated complexes. They do indicate that such species, if any, can exist only below pH 2. The pH dependence of the electronic spectra for the system Pd^{2+}–ts-β-ala cannot be followed below pH 3.5 since even using the minimum metal concentration needed for observing the d–d band (5×10^{-4} mol dm^{-3}) precipitation occurs. The spectral features in the range pH 9–3.5 are very similar to those for the system with ts-α-ala, the only difference being a less-pronounced band at 430 nm in the low-pH limiting spectrum.

NMR Spectra.—The low-frequency region of the ^{1}H NMR spectrum of the crystalline $Na_2[Pd(bs\text{-}\alpha\text{-}alaNO)_2]$ complex dissolved in D_2O is shown in Fig. 3(*a*). It contains two doublets corresponding to the methyl group of the amino acid indicative of the presence of two species in slow exchange on the NMR time-scale. The pH of the samples was then lowered to about 1.5 and the spectra recorded at increasing pH. Two different methyl doublets appear under strongly acidic conditions [Fig. 3(*b*)]. Upon increasing the pH these doublets simultaneously decrease in intensity until they disappear at slightly above pH 4. The low-frequency doublet (a) shows chemical shift values and a pH dependence typical of the deprotonation of the carboxylic group of the free amino acid. The decrease in intensity of the above doublets is paralleled by the appearance and subsequent growth of three new pairs of resonances (c–e in Fig. 3), two of which (c and d) correspond to the doublets present in the spectrum of the crystalline complex as dissolved, with a different intensity ratio. The frequency of all these doublets is slightly pH-dependent. It is worth noting that the spectral features of the complex as dissolved (around neutral pH) [Fig. 3(*a*)] are not completely matched by those obtained at the end of the titration [Fig. 3(*c*)] as far as the intensity ratio is concerned. The same spectral behaviour is observed for the complex $Na_2[Pd(ts\text{-}\alpha\text{-}alaNO)_2]$ with only minor differences in the chemical shift of the methyl resonances.

The spectrum at the lowest pH in Fig. 3, which is close to the end-point of the first titration step in the electronic spectra, contains signals of the free amino acid (doublet a) and of a complex species (doublet b). These peaks are then replaced by new resonances in a pH range corresponding to that of the second equilibrium in the electronic spectra. This spectral behaviour strongly suggests the assignment of doublet b and doublets c–e to species containing one and two bidentate nitrogen-deprotonated ligand molecules, respectively. In particular, d should correspond to the $[Pd(LNO)_2]^{2-}$ species of the crystalline complex, namely that with the ligands in a *trans* configuration. Since the polarographic analysis reveals the presence of only one species with a ligand-to-metal ratio of 2:1, we propose that the doublet c arises from the *cis* isomer. It is apparent that the interconversion between these isomers takes place only to a minor extent upon dissolution of the crystalline *trans* species [Fig. 2(*a*)]. We assign the additional species corresponding to the doublet e to a hydroxo species $[Pd(LNO)_2(OH)_x]^{(2+x)-}$ (x = 1 or 2) on the basis of the remarkable pH dependence of this doublet, and the well known tendency of Pd^{2+} to bind OH^- ions at very low pH.[11]

The pH dependence of the ^{1}H NMR resonances of the system Pd^{2+}–bsgly is shown in Fig. 4. Spectra were taken by the above procedure. Also in this case we observe equilibria between different species in slow exchange on the NMR time-scale. Peak a shows a pH dependence typical of deprotonation of the carboxylic group of the free amino acid, so it can be assigned to the methylene resonance of unligated bsgly. Its intensity

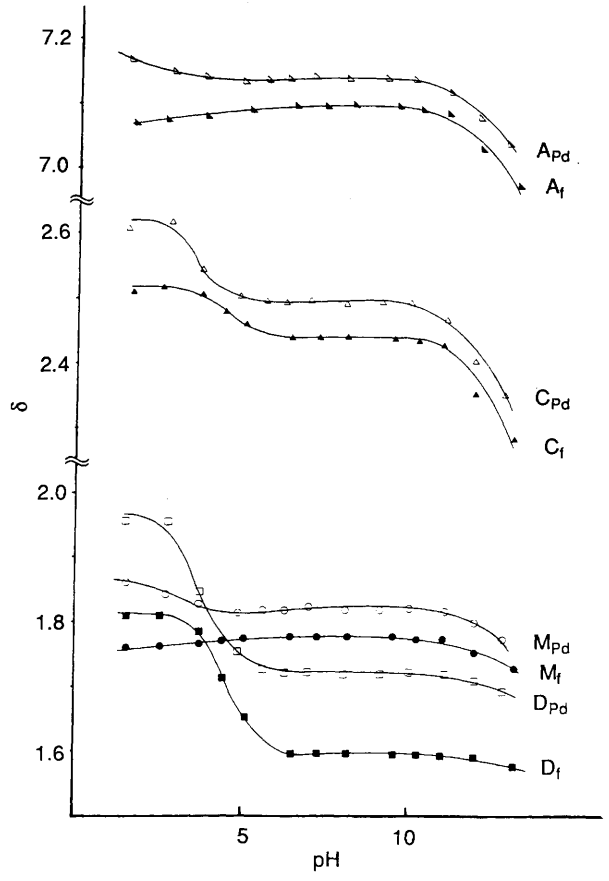

Fig. 5 The pH dependence of selected ligand resonances in the 400 MHz ^{1}H NMR spectrum of $[Pd(ts\text{-}\beta\text{-}alaNO)_2]^{2-}$ in D_2O: A, AA'BB' aromatic multiplet; M, methyl group of the N-protecting tosyl group; C and D, central peaks of the two methylene triplets; the indexes f and Pd indicate resonances of the free and Pd^{2+}-bound amino acid, respectively

decreases with increasing pH, until it disappears at pH 6. Resonance c is the major one in the limiting spectrum at low pH. With increasing pH it moves toward lower frequencies and its intensity decreases. At pH 3.5 it overlaps with peak d and the resulting resonance becomes the most intense signal in the spectra at higher pH. A set of two minor CH_2 peaks (b) is present at low pH and disappears at pH about 4. Resonance e is another minor peak appearing at pH about 3.5. The limiting spectrum at high pH is identical to that of the initial solution obtained by dissolving the crystalline complex. The major peak at low pH, c, is assigned to the [Pd(LNO)] species, while peak d most probably corresponds to $[Pd(LNO)_2]^{2-}$. It appears that the former peak shows an opposite and more pronounced pH dependence than that in the corresponding bs-α-ala spectrum. Moreover, in this case there is no spectral evidence for a *cis–trans* equilibrium involving the $[Pd(LNO)_2]^{2-}$ species. By analogy with the former case, peak e is assigned to a hydroxo species $[Pd(LNO)_2(OH)_x]^{(2+x)-}$. The additional minor peaks (b) present at low pH are tentatively assigned to carboxylate complexes.

Unlike the above cases, the pH-dependent ^{1}H NMR spectral features for the system Pd^{2+}–ts-β-ala are typical of a rapid exchange of the amino acid between free and metal-bound states. The pH dependence of the amino acid resonances in the presence and absence of Pd^{2+} is shown in Fig. 5. The methylene signals of the free amino acid (C_f and D_f) titrate with an apparent pK_a value of 4.5 corresponding to deprotonation of the carboxylic group. Above pH 11.5 all the peaks undergo a low-frequency shift most probably due to sulfonamide nitrogen deprotonation. Since the aromatic moiety is conjugated to the amide nitrogen through the SO_2 group,[12] the resonances of the N-protecting group (A and M) are also affected by ionization of the carboxylic group and of the amide nitrogen. If Pd^{2+} is added to the amino acid at pH about 13, with a final acid-to-metal ratio of 4:1, and the pH is decreased, two titration steps are still observed, one at high pH closely similar to that of the free amino acid and the other with an apparent pK value of 3.7. We assign both titration patterns to deprotonation of the sulfonamide nitrogen of the ligand: in particular, the low-pH equilibrium should correspond to that promoted by the metal, and the subsequent one to that of the excess of amino acid. Since a rapid exchange on the NMR time-scale is operative, and there is an excess of ligand, the effect of the nitrogen-deprotonation equilibrium and of metal co-ordination on the amino acid resonances coexist with that of deprotonation of the carboxylate group of the free amino acid. This makes the observed pK_a of 3.7 for the metal-promoted nitrogen deprotonation an upper limit.

Discussion

The polarographic curves obtained for N-sulfonyl-α- and β-alanines are similar and do not show appreciable differences from those previously obtained for the glycine derivatives. This indicates that the co-ordinative behaviour of these amino acids is the same above pH 3.5. The overall stability constants for the nitrogen-deprotonated complexes follow the order α-ala > gly > β-ala (see Table 1) which can easily be related to the electron-donor effect of the methyl group added to the glycine moiety and to the unfavourable formation of a six-membered chelate ring for the β-alanines.

Electronic and ^{1}H NMR spectra allow an insight into the low-pH co-ordination mode of these amino acids. The main points can be summarized as follows. (*i*) The first amino acid molecule binds to Pd^{2+} in the dianionic form at outstandingly low pH values. Nevertheless, the apparent pK_{NH} value of about 1 is in line with that of 2 evaluated for Pd^{2+}-promoted amide-nitrogen deprotonation in small peptides,[13] owing to the more acidic character of the sulfonamide as compared to the peptide nitrogen. (*ii*) Both techniques then confirm the equilibrium between nitrogen-deprotonated species bearing one and two amino acid molecules. (*iii*) In particular, in the Pd^{2+}–bs-α-ala system the two geometric isomers appear to form in equimolar amounts starting from strongly acidic pH values, although the *trans* isomer slightly prevails under conditions close to neutrality. On the other hand, the NMR spectra taken upon stepwise lowering of the pH of solutions of the crystalline *trans*-$[Pd(LNO)_2]^{2-}$ species from the initial neutral value down to pH of about 3.5 indicate only a minor *trans* to *cis* interconversion. This means that the *cis* isomer can form only at low pH values, namely only in the presence of the precursor [Pd(LNO)], and that the above isomerization process is kinetically controlled. The separation of the *trans* isomer in the solid state (see Part 1)[1] is reasonably due to the presence of a favourable *trans* to *cis* ratio in solution, and to its lower solubility. A *cis–trans* equilibrium is probably present also in the bsgly system, but the methylene groups of this ligand appear to be much less sensitive to the molecular arrangement than are the methyl groups of the α-alanines. (*iv*) Proton NMR spectroscopy allows one to address the question of whether the formation of the nitrogen-deprotonated complexes passes through the preliminary formation of species in which the ligands act as simple carboxylates, as previously found for Cu^{2+} and Cd^{2+}.[3,4] The role of these precursor complexes is thought to be to prevent metal hydroxide precipitation and to increase the acidity of the amide nitrogen through an inductive effect.[3,4] For the present systems involving N-protected α-alanines we have obtained no spectral evidence for the presence of carboxylate complexes, while with bsgly they possibly appear as minor species: this is consistent with the lower stability of the nitrogen-deprotonated complexes for this ligand as compared to the N-protected α-alanines. In the *N*-sulfonyl-β-alanine

systems, where carboxylate complexes should be much more stable than those of the corresponding α-amino acids,[14] rapid exchange on the NMR time-scale between the free and metal-bound amino acid prevented the observation of the individual species at low pH. Overall, it can be reasonably proposed that the Pd^{2+} ion possesses such an intrinsic outstanding ability to substitute for the protons of the amide and carboxylic groups of the amino acids as to decrease the two pK_a values to comparably low values. In this context of simultaneous equilibria the role of the carboxylate complexes cannot be unambiguously defined, although it is apparent that the above two-step mechanism involving a primary metal ligation through the formation of stable carboxylate complexes prevailing in a determined pH range cannot apply to the present systems. These species could be at most considered as transient intermediates in a concerted mechanism which drives the formation of the nitrogen-deprotonated species through metal substitution for two protons of the amino acid molecule at remarkably low pH values. (*v*) Finally, *N*-acetyl-, *N*-benzoyl- and *N*-benzyloxycarbonyl-glycine appear unable to form stable nitrogen-deprotonated complexes with Pd^{2+}, as previously observed with Cu^{2+} and Cd^{2+}. The weak metal interaction in the range pH 3.5–4.2 may possibly involve the formation of carboxylate complexes, but it cannot be unambiguously characterized.

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